

REMARKS

Claims 1-17, 19-21, 23-25 and 30 are pending in the above-identified application.

Unity/Election Requirement

Applicant respectfully maintains a traversal of the Unity/Election Requirement for the reasons stated in the Response filed June 23, 2010, which reasons are deemed repeated herein. Applicant would consider cancelling claims directed to compound XX if this would facilitate or accelerate the present prosecution.

Issues under 35 USC 103(a)

Claims 1, 2, 9, 10, 12-14, 16, 19-21 and 23-25 have been rejected under 35 USC 103(a) as being unpatentable over Calverley (Tetrahedron, Vol. 43, No. 20, 1987, pp. 4609-4619). This rejection is respectfully traversed based on the following reasons.

Distinctions over Calverley

Calverley is discussed at pages 1-2 of the specification. Significant distinctions exist over this reference as compared to the presently claimed invention. It is first noted that the method of the present invention provides for the introduction of a specific 24-keto-26,27-cyclo vitamin D side chain onto vitamin D-C₂₀-aldehydes (or a precursor thereof with an aldehyde group in the position corresponding to position 20 of the vitamin D final product), which significantly results in advantages for employment of this method on a more efficient production scale. As stated in the specification on page 2, lines 6-13, the known process described by Calverley using the phosphorane reagent IV had two major disadvantages:

(1) During the C=C-bond forming reaction, triphenylphosphine oxide is formed as a side product which is difficult to remove from the reaction mixture. Thus, the formation of triphenylphosphine oxide disadvantageously added an additional chromatographic step to the process.

(2) The Wittig reaction employed in the Calverley process furthermore necessitated reaction temperatures above 95°C due to the low reactivity of the phosphorane IV. This high temperature is disadvantageous on an industrial scale due to energy consumption.

As stated on page 7, lines 4-10 in the specification, the novel process of the present invention, also called Wadsworth-Emmons, Wittig-Horner, or Horner-Emmons-Wadsworth reaction, surprisingly solves the problems noted above:

(1) The phosphorus side product of the reaction is a phosphate ester, and hence soluble in water, unlike the undesired triphenylphosphine oxide, which advantageously allows for easier separation of the phosphate ester from the reaction mixture, simply by aqueous extraction from the reaction mixture. Since chromatographic separations are tedious and expensive on a production scale, this means a significant improvement to the process, especially on an industrial scale.

(2) The reagent of general structure VII is advantageously more reactive than the corresponding phosphorane allowing for the usage of mild reaction conditions such as a significantly lower temperature, typically below 35°C. Lower reaction temperatures save energy and thereby costs which again is especially relevant on an industrial scale. Furthermore, the formation of by-products increases with increasing temperature. By running the reaction significantly lower than the reaction temperature required for the Wittig reaction, the formation of undesired by-products and decomposition could be reduced with the novel process of the present invention.

In addition to the above, the process of the present invention surprisingly results in an increased yield.

Comparative results are listed in the following Table for illustration:

Process	Wittig / phosphorane IV	Wittig / phosphorane IV	Wittig-Horner / phosphonate VII	Wittig-Horner / phosphonate VII
Reference	THL Calverley page 4616, 3 rd example	WO 87/00834 Preparation 19	WO 2005/095336 Example 1	presently used industrial process
Yield	63 %	not disclosed	81 %	>72 %
Reaction temperature	105°C	95 - 105°C	15 - 30°C	below 35 °C
Work-up / removal of side product	chromatography	chromatography	aqueous (basic) extraction	aqueous (basic) extraction

Calverley fails to disclose or suggest using the specific keto-phosphonate VII employed in the presently claimed invention. Calverley further fails to recognize the above-noted advantageous features of the presently claimed invention (e.g. the omitted chromatography step, increased yield, lower reaction temperature), such that significant patentable distinctions exist over this reference. Calverley additionally fails to recognize the unexpected, advantages achieved by the process of the presently claimed invention, especially when it is employed on an industrial scale. Thus, the above rejection must be withdrawn.

If any questions arise regarding the above matters, please contact Applicant's representative, Andrew D. Meikle, in the Washington Metropolitan area at the phone number listed below.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

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Respectfully submitted,

By 

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